REMARKS

In a non-final Office Action dated January 23, 2006 the Examiner in charge of the above-noted application maintained the rejection of Claims 1-12 and 17 under 35 U.S.C. §103. Claims 13-16 are withdrawn from consideration for being directed to non-elected subject matter. Applicants respond by submitting a Supplemental Declaration of Dr. Alan Attie and the comments set forth hereinbelow, and respectfully request reconsideration of the merits of this patent application.

Rejection under 35 U.S.C. 103(a)

The rejection of Claims 1-12 and 17 under 35 U.S.C. 103(a) is maintained. In this regard, the Examiner asserts that the Declaration filed on November 18, 2005 under 37 CFR 1.131 has been considered but remains ineffective to overcome Twisk et al. (*The Journal of Clinical Investigations*, Volume 105, Number 4, page 521, February 2000). Specifically, the Examiner asserts that the Declaration is not clear as to Mr. Paul Bates' inventive contribution to the claimed invention.

In an effort to expedite prosecution on the merits, applicants submit herewith a Supplemental Declaration of Dr. Alan D. Attie, co-inventor of the present patent application and a co-author of Twisk et al. In the Supplemental Declaration, Dr. Attie supplements his prior declaration that Mr. Bates was named as an inventor of the patent application because of his intellectual contribution to many of the details of the execution of this invention, some of which are encompassed by claims presently in the application.

The Supplemental Declaration makes clear that Mr. Bates came up with the idea of reducing the invention to practice through the use of a vector-based delivery system. This contribution is encompassed within the pending claims, which recite for example, delivering a genetic construct into the vein of the mammal such that the expression and production of the fusion protein in the mammal results in lower serum cholesterol. Dr. Bates' contribution is also exemplified at pages 8-9 of the specification, which describe *in vivo* experiments where cholesterol levels were lowered by at least 20%. The striking success of this strategy was not fairly predictable from the literature due to uncertainties associated with *in vivo* delivery of genetic material.

The Supplemental Declaration of Dr. Attie also makes clear that Twisk et al. explores the relationship between the presence of the LDL receptor and lipoprotein secretion in hepatocytes from both wild-type and LDL receptor-deficient mice. Twisk et al. treats hepatocytes with recombinant adenoviruses to overexpress the LDL receptor in *Ldlr-/-* cells, resulting in degradation of approximately 90% of newly synthesized apoB100. (See Twisk et al., Abstract, pg. 524, col. 1; pg. 526, col. 2; Figs. 5 and 6). Twisk et al. does not suggest *in vivo* delivery of genetic material to lower serum cholesterol levels. Thus, applicants submit that the contributions of Mr. Bates particularly in regards to the gene delivery system described in the claimed invention are not obvious and go well beyond the disclosure of the Twisk paper.

In this regard, applicants further submit that there are multiple uncertainties and numerous technical hurdles that were overcome in attempting to successfully deliver genetic material into the vein of an animal. These hurdles include for example, inadequate gene delivery systems, complexities of cell targeting and cellular localization of the genetic material to achieve the desired effect of lowered cholesterol. Solutions for overcoming these hurdles cannot be predicted from Twisk et al. One of ordinary skill in the art would readily appreciate the significant differences between the experiments that Twisk conducted, (i.e., treating cells with a genetic material in a controlled *in vitro* environment) versus the pioneering *in vivo* experiments conducted by the inventors, (i.e., gene therapy that was effective for its intended purpose). Accordingly, it is believed that the submission of this Supplemental Declaration will overcome the Examiner's rejection.

Next, the Examiner asserts that if the third inventor, Mr. Paul Bates, contributes to the difference between the instantly claimed invention and the disclosure of Twisk et al. applicants must also provide evidence/arguments to explain why such modification is not obvious in view of the combined teaching of Twisk et al., Teasdale and Jackson, and presumably Attie et al. (U.S. Pat. No. 5,521,071).

In response, applicants wish to reintroduce the notion that while the expectations and the promise of gene therapy are great, the process remains unpredictable. Many *in vivo* experiments fail to achieve the desired result because there are still major difficulties such as, shortcomings in gene delivery systems and inadequate understanding of the biological interaction of delivery systems with target cells. Indeed, it was not clear prior to the work of the applicants here that the

described genetic construct could be delivered into the vein of an animal to effectively lower serum cholesterol. However, applicants were able to successfully demonstrate that delivery of the claimed genetic construct into the vein of an animal can result in lower LDL levels in the blood stream. Applicants showed that the experiments worked in spite of the uncertainties typically associated in conducting *in vivo* gene therapy. The success of this strategy could not fairly have been predicted from the documents cited by the Examiner. Thus, applicants submit that until the work described here, the claimed invention was not obvious.

Turning to the specific documents cited by the Examiner, applicants submit that Twisk et al. as discussed above does not contemplate *in vivo* gene delivery. It simply reports studies on the effects of LDL receptor overexpression and lipoprotein secretion in a controlled environment of hepatocytes. Thus, Twisk does not render the claimed invention obvious.

Likewise, Teasdale and Jackson is simply a review article that broadly discusses signal-mediated sorting of membrane proteins between the endoplasmic reticulum and the golgi apparatus. It does not suggest a gene delivery system to lower cholesterol. The paper does recite that some proteins tagged with the receptor KDEL are retained in the ER by virtue of the signal peptides. However, it is far from clear that this phenomenon would be effective for all proteins, particularly for non-native proteins such as a truncated and soluble LDL receptor to which a signal peptide has been attached. In fact, it suggests that chimeric protein molecules are often modified in the golgi apparatus of the cell, which teaches away from the notion that the genetic material is localized tot eh ER as recited in the claimed invention (see pg. 40 of Teasdale and Jackson).

The Attie patent (5,521,071) discloses that the truncated LDL receptor will bind to LDL. It does not disclose what portion of the entire LDL receptor protein is responsible for the effect on apoB levels (see Fig. 1 of the '071 patent). It discloses that the truncated portion of the LDL receptor gene can be expressed in insect cells. The '071 patent does not suggest a route of delivering genetic material into a mammal to yield the desired effect of lowered serum cholesterol.

Thus, applicants submit that they discovered the invention only works when the LDL receptor is localized in the secretory pathway where the apoB is processed. To do this, the LDL receptor had to be localized in the ER. This had not been done before. While the localization

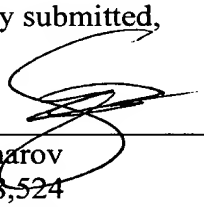
domains for the ER were known before, whether or not this level of localization would be sufficient to locate the LDL receptor, where it could interact with apoB, was unknown. It was not clear at all if the ER was the right place in the secretion pathway for trapping apoB. Despite, any lack of suggestion for the literature, applicants identified an inventive route of delivery and demonstrated that it was effective in lowering serum cholesterol in mammals. This was a highly specific result.

In summary, applicants submit that the combination of the uncertainty arising in general with techniques of genetic engineering, and the uncertainty inherent in dealing with a complex biological system such as cholesterol secretion, makes it unpredictable that the method described by the applicants here would actually work. Thus, there was no motivation or reasonable expectation that combining the cited documents would be successful in advance of applicants' claimed invention.

Accordingly, applicants respectfully request that in view of the supplemental Declaration and comments, the rejection be respectfully reconsidered and withdrawn, and that a timely Notice of Allowance be issued in this case.

A petition for a one-month extension of time is enclosed. No other fees are believed due in regard to this submission. If any other fee is due or any other extension of time is required in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the petition fee to the Deposit Account No. 17-0055.

Respectfully submitted,



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